

# Healthcare Utilization and Cost Effects of Prior Authorization for Pregabalin in Commercial Health Plans

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**H**ealth plans and government-sponsored healthcare programs have been under constant and increasing pressure to balance costs of care with improved health outcomes and high-quality care.<sup>1-3</sup> This is particularly true for managing prescription drug expenditures, one of the most visible sectors of healthcare spending.<sup>4-6</sup> Various measures intended to strike that balance, including generic substitution, tiered copayment or cost sharing, step therapy, and prior authorizations (PAs),<sup>7-9</sup> have been widely adopted by health plans and pharmacy benefit managers. Prior authorization, a requirement to obtain prior approval from the health plan or pharmacy benefit manager for prescription medication reimbursement, is recognized for its potential as an effective tool for encouraging appropriate and cost-effective drug utilization, reducing unnecessary prescription drug use, and controlling expenditure growth.<sup>1,10</sup> However, recent studies<sup>11-19</sup> have shown mixed evidence on the overall effect of PA policies, with some documenting potential for savings and others showing negative clinical and economic effects. Given the administrative costs of running the PA programs and the burden they put on healthcare providers (physicians, nurse practitioners, and pharmacists) and patients, managed care organizations are prudent to evaluate whether their PA programs are meeting the intended objectives.<sup>20-23</sup>

In a prior study, Margolis et al<sup>24</sup> investigated the effect of PA policies on Medicaid patients diagnosed with postherpetic neuralgia (PHN) or having neuropathic pain associated with diabetic peripheral neuropathy (pDPN), comparing states with versus without such PA policies. Neuropathic pain associated with diabetic peripheral neuropathy, a complication of diabetes mellitus,<sup>25,26</sup> and PHN, a complication of herpes zoster infection,<sup>27,28</sup> are 2 neuropathic pain conditions that share common pharmacologic treatments, including opioids, antidepressants, and anticonvulsants.<sup>28-36</sup> Although pregabalin (Lyrica [schedule V]; Pfizer Inc, New York, NY) is one of the medications indicated for and recommended as first-line treatment in pDPN and PHN,<sup>34-41</sup> many health plans have restricted access to it by requiring PA for reimbursement. The study by Margolis et al<sup>24</sup> found that, although state Medicaid programs' pregabalin PA requirements accomplished the objective of lower pregabalin utilization, they were associated with the unintended effects of increased opioid use and disease-related healthcare costs. Because that study was undertaken in a Medicaid

**Objectives:** To compare changes in medication use and costs over time for management of painful diabetic peripheral neuropathy (pDPN) or postherpetic neuralgia (PHN) among patients in commercial health plans requiring prior authorization (PA) for pregabalin versus patients in plans without pregabalin PA policies.

**Study Design:** Retrospective claims data were obtained for 2005 to 2007 from 6 health plans with pregabalin PA and 6 health plans without pregabalin PA. Differences in resource utilization and costs were compared between baseline and 1-year follow-up periods using a pre-post parallel-group design.

**Methods:** Adults diagnosed as having pDPN or PHN with at least 1 claim for pDPN- or PHN-specific pain medication were selected. Pharmacologic therapy, healthcare utilization, and expenditures were analyzed using bivariate statistics and generalized linear models via a difference-in-differences approach comparing cohorts year over year.

**Results:** The 2 cohorts included 2084 patients in PA plans and 1320 patients in non-PA plans. Compared with non-PA plans, plans requiring PA experienced a 5.0-percentage point lower increase in patients using pregabalin year over year ( $P < .001$ ). Utilization in PA plans of other anticonvulsants was 3.7 percentage points higher ( $P = .03$ ), while nonopioid analgesic use was 5.2 percentage points lower ( $P = .01$ ). There were no significant differences in opioid, antidepressant, or other pDPN or PHN medication use or pDPN- or PHN-related total healthcare costs.

**Conclusion:** A PA policy for pregabalin was associated with lower pregabalin utilization, but there was no statistically significant effect on pDPN- or PHN-specific medication or healthcare expenditures.

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### Take-Away Points

This study compared healthcare utilization and expenditures between health plans with versus without a prior authorization (PA) policy for pregabalin.

- Plans with PA had significantly lower proportions of patients with any pregabalin use.
- Plans with PA experienced higher use of other anticonvulsants; lower use of nonopioid analgesics; no differences in the use of opioids, antidepressants, or other painful diabetic peripheral neuropathy (pDPN)- or postherpetic neuralgia (PHN)-specific drugs; and no net cost effect.
- Although the PA policy accomplished the objective of controlling access to pregabalin, there were no statistically significant differences in pDPN- or PHN-specific medication or healthcare expenditures.

use in health plans is associated with higher overall and disease-related healthcare service utilization and expenditures for the management of pDPN or PHN.

### Data Source

Years 2005-2007 of the Thomson Reuters MarketScan Commercial Claims and Encounters Database were used for this study. This database in-

cludes complete longitudinal records of inpatient services, outpatient services, long-term care, and prescription drug claims covered under various fee-for-service and capitated health plans, including exclusive provider organizations, preferred provider organizations, point-of-service plans, indemnity plans, and health maintenance organizations. Retrospective data were obtained from 12 commercial health plans, 6 that had implemented PA around the time pregabalin was launched and 6 with no known restriction on reimbursement for pregabalin. Plans with step therapy, quantity limits, or formulary restrictions other than PA were not included. Plans with tiered formularies were included. Health plan restrictions (PA, step therapy, etc) were not examined for pDPN- or PHN-related medications other than pregabalin. The health plans' identities cannot be divulged because of contractual arrangements involved in acquiring their data.

population among whom patient characteristics and policies are likely to differ from those in commercial health plans, the present study was undertaken to investigate the effect of a pregabalin PA policy among commercially insured patients with pDPN and PHN.

The primary objective of this study was to investigate the overall effect of PA policies restricting access to pregabalin on utilization of pregabalin and other pharmacologic therapies. We also evaluated the difference in overall healthcare utilization and associated direct costs for the management of pDPN or PHN between patients in commercial health plans with versus without PA policies for pregabalin.

METHODS

### Study Design

The intervention evaluated was the introduction of a restriction on the use of pregabalin for the treatment of pDPN and PHN in the form of PA compared with unrestricted access to pregabalin for these indications. The effect of PA was assessed in commercial health plans using a pre-post parallel-group design. Calendar year 2005 was designated as the baseline (preindex) period. A 6-month PA initiation window followed the baseline period. The 1-year postindex follow-up period began on July 1, 2006, and ended on June 30, 2007. The study sample was limited to patients with a diagnosis of DPN or PHN at any point from 2005 to 2006. Evidence of treatment for symptomatic relief of DPN or PHN pain was required as a proxy for pDPN (all PHN is acknowledged as painful). Utilization and expenditure data were compared between the baseline and follow-up periods for the 2 cohorts of health plans with versus without PA for pregabalin.

The study tested the following 3 hypotheses: (1) Access restrictions to pregabalin in the form of PAs are associated with lower utilization of pregabalin relative to a comparable population without such restrictions. (2) The use of PA for restricting pregabalin use in health plans is associated with higher utilization of other pharmacologic treatments for pDPN or PHN. (3) The use of PA for restricting pregabalin

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### Subject Selection

Patients were required to be a minimum of 18 years of age and continuously enrolled in the health plan with both medical and pharmacy benefits from January 1, 2005, through June 30, 2007. They were required to have at least 1 claim with an *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnosis code for DPN (250.6x or 357.2x) or PHN (053.1x) at any point from 2005 to 2006 and at least 1 claim within 60 days after a DPN or PHN diagnosis from 2005 to 2006 for a medication used in treating pDPN or PHN (**Table 1**) or for a pain intervention procedure (**Table 2**). Patients with pDPN or PHN were analyzed as one group because of the small PHN sample size (in both cohorts, approximately 86% of patients had only pDPN).

Patients with Medicare coverage were excluded to represent the perspective of a commercially insured employed population. Patients were also excluded if they had resided in a long-term care facility for 90 days or longer or if they had any claims with an *ICD-9-CM* diagnosis code for epilepsy (345.xx or 780.39), 1 inpatient or 2 outpatient nondiagnostic claims for cancer (140.xx-172.xx, 174.xx-208.xx, or 235.xx-239.xx, except basal cell and squamous cell skin cancers and

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■ **Table 1.** Medications Used for Treating pDPN and PHN

Medication Class	Generic Name
Nonopioid analgesics, Rx only	Celecoxib, diclofenac, etodolac, fenoprofen, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac tromethamine, mefenamic acid, meloxicam, nabumetone, naproxen, naproxen sodium, oxaprozin, piroxicam, sulindac, tolmetin sodium
Opioid analgesics	Buprenorphine, codeine, dihydrocodeine, fentanyl, hydrocodone, hydromorphone, levorphanol tartrate, meperidine, methadone, morphine sulfate, oxycodone, propoxyphene, tramadol, combinations (with acetaminophen, aspirin, etc)
Anticonvulsants	Carbamazepine, gabapentin, lamotrigine, oxcarbazepine, phenytoin, pregabalin, topiramate, valproate sodium, valproic acid
Tricyclic antidepressants	Amitriptyline, desipramine, doxepin, imipramine, nortriptyline
Other antidepressants	Bupropion, citalopram, duloxetine, paroxetine, trazodone, venlafaxine
Other	Baclofen, capsaicin cream, clonidine, diclofenac cream, lidocaine mexiletine, lidocaine patch, pamidronate, prilocaine cream, or tizanidine

pDPN indicates painful diabetic peripheral neuropathy; PHN, postherpetic neuralgia.

■ **Table 2.** Pain Intervention Procedures

Intervention	CPT Codes	ICD-9-CM Procedure Codes
Physical therapy	97001, 97002	—
Acupuncture	97801, 97811, 97813, 97814	99.92
Introduction of anesthetic agent, nerve block	64400-64530	04.8-04.89 or 05.31
Neurostimulators	63650, 63655, 63685, 64550-64595	03.93, 04.92, or 86.94-86.96
Nerve destruction by neurolytic agent	64600-64680	03.8x or 04.2x
Nerve decompression	64722-64727	04.4x

CPT indicates Current Procedural Terminology; ICD 9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification.

benign neoplasms), or transplant surgery (codes available on request from the corresponding author) at any point during the study period. **Table 3** summarizes the incremental attrition associated with each of these criteria and the resulting cohort sample sizes for PA and non-PA health plans.

### Study Analysis Period

The study analysis period began on January 1, 2005, and ended on June 30, 2007. Calendar year 2005 was used as a baseline period. A 6-month PA initiation window from January to June 2006 followed the baseline period to minimize possible misclassification of data when the exact starting dates of the PA policies were not known and in recognition of the fact that the implementation date for PA would vary across plans. The 1-year postindex follow-up period ran from July 1, 2006, through June 30, 2007. The use of 1 year of follow-up data was chosen to provide equal lengths in the preindex and postindex periods. Pregabalin was approved for treatment of pDPN and PHN in the United States in September 2005; however, the volume of claims for the few patients receiving pregabalin in 2005 (3.7% of patients) was low (1.7 prescription claims per patient receiving pregabalin).

### Outcome Measures

Diagnoses and pharmacologic therapy were derived from medical and pharmacy claims received according to service dates in the study period. Drugs for treating pDPN or PHN were analyzed by drug class as summarized in Table 1 and for pregabalin individually. The pDPN or PHN diagnoses and comorbidities were determined from nondiagnostic medical claims.

Healthcare utilization data included hospital admissions, length of stay, emergency department visits, physician office visits, other outpatient services, and numbers of outpatient prescriptions by class and for pregabalin individually. Expenditures were adjusted to 2007 constant US dollars, measured as the gross covered payments for all healthcare services or products (ie, the amount eligible for payment after applying pricing guidelines such as fee schedules and discounts and before applying deductibles, copayments, and coordination of benefits). Utilization and expenditures were measured for all medical and pharmacy claims. Medical claims were designated as DPN or PHN specific when a diagnosis for DPN or PHN appeared in any position in the claim.

■ **Table 3. Sample Size Attrition**

Attrition Criterion Between January 1, 2005, and June 30, 2007, Unless Otherwise Noted	Non-PA Plans	PA Plans
DPN or PHN diagnosis between January 1, 2005, and December 31, 2006	6337	7258
Exclusions for epilepsy, cancer, transplant surgery	6058	6915
<90 d total in a long-term care facility	6013	6882
Age ≥18 y at the beginning of 2005	5973	6849
Continuous health plan eligibility	2321	3564
Final cohort with DPN or PHN pain medication or procedure within 60 d of diagnosis	1320	2084
No. of patients in the final cohort receiving pregabalin during the postindex follow-up period	244	208

DPN indicates diabetic peripheral neuropathy; PA, prior authorization; PHN, postherpetic neuralgia.

### Statistical Analysis

Bivariate descriptive statistics were used to characterize the study population in terms of all key dependent, independent, and control variables by year. All dependent and independent variables were compared in the 1-year postindex period (July 1, 2006, to June 30, 2007) with the 2005 baseline within cohort, and the year-over-year differences were contrasted between cohorts as follows: Difference in Differences = (Restricted Cohort 2006-2007 – Restricted Cohort 2005) – (Unrestricted Cohort 2006-2007 – Unrestricted Cohort 2005).<sup>42,43</sup>  $\chi^2$  Tests were used to evaluate differences for categorical variables, and *t* tests were used for continuous variables. Tests for statistically significant differences in outcome variations of PA plans versus non-PA plans before and after the intervention (difference in differences) were conducted. A significance level of .05 was used to determine statistical significance.

Multivariable analyses were used to explore the association between PA restrictions for pregabalin and the outcomes of interest. A logit model was used to compare pregabalin use in the postindex period between the plans with versus without PA restriction. The logit model used a dichotomous outcome variable indicating the use of pregabalin in the postindex period and a stochastic error term to capture nonsystematic variation. The independent variable of interest was the indicator for enrollment in a health plan with a PA policy.

Generalized estimating equation models were used to test the hypotheses of differential increments in outcomes between plans with versus without PA after controlling for the potential confounding effects of age, sex, geographic region, health plan type, other chronic pain conditions, and comorbidities. Cluster units were defined at the individual level because a given patient contributed data to the preperiod and postperiod. The following outcomes were included in the analysis: opioid use, nonopioid analgesic use, other pDPN or PHN medication utilization, and pDPN- or PHN-related healthcare costs.

The key independent variables in the regressions included an indicator for enrollment in a health plan with a PA policy,

a time indicator (for 2006-2007 vs 2005), age, sex, geographic region, health plan type (health maintenance organization, preferred provider organization, point of service, or other), and a set of diagnostic flags to control for the effect of comorbidities. In linear regression models, the difference-in-differences estimate was the coefficient associated with the interacted term for a health plan with a PA policy and the period indicator. Because this coefficient has no direct interpretation in nonlinear models, the marginal effects of the interaction terms were calculated to express these effects across the multivariable models using the same units of measure as the original dependent variable (eg, probability of use, number of claims, and US dollars).<sup>44,45</sup>

Among the generalized estimating equation models, logit link and binomial variance functions were used for modeling opioid use. Log link and negative binomial variance functions were used for counts outcomes (ie, utilization of nonopioid and other pDPN or PHN medications). Log link and gamma variance functions were used for pDPN- or PHN-related costs. The variance functions for the generalized estimating equation models were verified based on the results of the modified Park test on the raw scale residuals. The exchangeable correlation structure was implemented and verified by the quasi-likelihood under the independence model criterion as the best working correlation structure. Analyses were conducted using STATA release 9 (StataCorp LP, College Station, TX).

## RESULTS

A total of 3404 patients met all subject selection criteria (Table 3), with 2084 patients in PA plans and 1320 patients in non-PA plans. In both cohorts, approximately 86% of patients were diagnosed as having DPN and approximately 14% as having PHN (Table 4). The PA cohort was slightly older (mean [SD] age, 52.3 [6.9] vs 51.6 [7.2] years, *P* = .004), with members residing primarily in the western and north central regions of the United States, compared with the non-PA cohort, whose

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■ **Table 4.** Sample Demographics

Demographic Variable as of the July 1, 2006, Index Date	Non-PA Plans (n = 1320)	PA Plans (n = 2084)	P
<b>Patient age, mean (SD), y</b>	51.6 (7.2)	52.3 (6.9)	.004
<b>Female sex, No. (%)</b>	715 (54.2)	1132 (54.3)	.93
<b>Deyo-Charlson Comorbidity Index, mean (SD)</b>	2.4 (1.8)	2.4 (1.7)	.95
<b>Geographic region, No. (%)</b>			
Northeast	77 (5.8)	16 (0.8)	<.001
North Central	197 (14.9)	595 (28.6)	<.001
South	878 (66.5)	354 (17.0)	<.001
West	163 (12.3)	1117 (53.6)	<.001
Other	5 (0.4)	2 (0.1)	.08
<b>Health plan type, No. (%)</b>			
Comprehensive	56 (4.2)	241 (11.6)	<.001
Health maintenance organization	54 (4.1)	986 (47.3)	<.001
Point of service	282 (21.4)	147 (7.1)	<.001
Preferred provider organization	904 (68.5)	710 (34.1)	<.001
Other	24 (1.8)	0	<.001
<b>pDPN or PHN diagnosis, No. (%)</b>			
pDPN only	1130 (85.6)	1794 (86.1)	.70
PHN only	187 (14.2)	286 (13.7)	.72
pDPN and PHN	3 (0.2)	4 (0.2)	.83

PA indicates prior authorization; pDPN, painful diabetic peripheral neuropathy; PHN, postherpetic neuralgia.

members were located mostly in the southern region. Insurance coverage differed between cohorts, with mostly preferred provider organization and health maintenance organization insureds in PA plans, while non-PA members had predominantly preferred provider organization coverage and point of service to a lesser extent. Sex distribution and preindex comorbidity were not significantly different between the 2 cohorts. Analysis of preindex medication use (antidepressants not used in pDPN or PHN treatment, anxiolytics, hypnotics, migraine medications, and muscle relaxants) also showed no statistically significant differences between cohorts.

Pregabalin use increased from 2.4% in 2005 to 10.0% during the postindex follow-up period among PA patients and from 5.7% to 18.5% among non-PA patients, representing increases of 7.5 and 12.8 percentage points, respectively, for a net unadjusted difference in differences between the groups of -5.3 percentage points ( $P < .001$ ), indicating that PA plans had a 5.3-percentage point lower net increase in postindex pregabalin use (Table 5). The adjusted estimate of the marginal effect from being in a PA plan (Table 6) was a 5.0-percentage point decrease in the probability of any pregabalin use during the postindex follow-up period relative to being in a non-PA plan ( $P < .001$ ).

Opioid analgesics were the most commonly used medications. The percentage of patients with opioid claims was not significantly different between preindex and postindex periods for either cohort, altering from 56.8% to 56.6% in PA plans ( $P = .91$ ) and from 52.3% to 54.3% in non-PA plans ( $P = .21$ ). The net 2.2-percentage point unadjusted difference-in-differences decrease among patients receiving opioids in PA plans year over year (Table 5) was not statistically significant ( $P = .29$ ). Multivariable modeling showed no differences in opioid use year over year between cohorts, with the marginal effect (Table 6) not statistically significant ( $P = .31$ ) for the adjusted 2.3-percentage point lower probability of opioid use in PA plans.

There were higher unadjusted preindex to postindex percentages of patients in PA plans using anticonvulsants other than pregabalin and gabapentin (1.8 percentage points,  $P = .02$ ) and significantly lower unadjusted percentages between preindex and postindex periods for nonopioid analgesics (4.0 percentage points,  $P = .04$ ) compared with patients in non-PA plans (Table 5). Unadjusted difference-in-differences metrics for gabapentin (2.2 percentage points,  $P = .16$ ), tricyclic antidepressants (1.5 percentage points,  $P = .22$ ), and other pDPN- or PHN-related medications (-1.9

**Table 5.** Unadjusted Differences in pDPN- and PHN-Related Prescription Utilization and Expenditures From the Preindex Period to the Postindex Period and Difference in Differences for PA Plans Minus Non-PA Plans<sup>a</sup>

Utilization and Expenditure Metric	Difference From Preindex Period to Postindex Period <sup>b</sup>		Difference in Differences <sup>c</sup>	
	Non-PA Plans (n = 1320)	PA Plans (n = 2084)	PA Plans Minus Non-PA Plans	P
<b>Outpatient pDPN or PHN Prescriptions</b>				
<b>Pregabalin</b>				
Patients with Rx claim, %	12.8	7.5	-5.3	<.001
Expenditures, \$	122	69	-53	<.001
<b>Gabapentin</b>				
Patients with Rx claim, %	-4.0	-1.8	2.2	.16
Expenditures, \$	-98	-111	-13	.37
<b>Other anticonvulsants</b>				
Patients with Rx claim, %	-1.7	0.1	1.8	.02
Expenditures, \$	4	10	6	.62
<b>Opioid analgesics</b>				
Patients with Rx claim, %	2.0	-0.1	-2.2	.29
Claims for patients with Rx claim	0.3	0.5	0.2	.68
Mean days supplied for patients with Rx claim	12.1	18.5	6.4	.82
Expenditures, \$	7	-1	-8	.81
<b>Nonopioid analgesics</b>				
Patients with Rx claim, %	-1.1	-5.1	-4.0	.04
Expenditures, \$	-33	-30	3	.78
<b>Tricyclic antidepressants</b>				
Patients with Rx claim, %	-3.8	-2.3	1.5	.22
Expenditures, \$	-1	-3	-2	.60
<b>Other antidepressants</b>				
Patients with Rx claim, %	2.7	0.9	-1.9	.17
Expenditures, \$	56	42	-14	.39
<b>Other</b>				
Patients with Rx claim, %	1.0	0.2	-0.8	.36
Expenditures, \$	0	0	0	.88
<b>pDPN- or PHN-related Expenditures, 2007 \$</b>				
Medication, \$	59	-20	-79	.09
Total, \$	45	-11	-56	.40

PA indicates prior authorization; pDPN, painful diabetic peripheral neuropathy; PHN, postherpetic neuralgia.

<sup>a</sup>Expenditures represent the mean per member per year.

<sup>b</sup>Difference from the preindex period to the postindex period is the postindex result minus the preindex result.

<sup>c</sup>Difference in differences represents the PA plan difference from the preindex period to the postindex period minus the non-PA plan difference from the preindex period to the postindex period.

percentage points,  $P = .17$  for other antidepressants; and  $-0.8$  percentage points,  $P = .36$  for other oral pDPN or PHN medications) showed no statistically significant differences between PA and non-PA cohorts year over year. Multivariable analysis demonstrated a similar statistically significant 3.7–percentage point higher probability ( $P = .03$ ) of patients

in PA plans using anticonvulsants (exclusive of pregabalin) and a 5.2–percentage point lower probability ( $P = .01$ ) of their using nonopioid analgesics (Table 6) compared with patients in non-PA plans.

As summarized in Table 5, expenditures per plan member for pregabalin (unadjusted) were lower by \$53 ( $P < .001$ ) year

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**Table 6.** Marginal Effects of Utilization Variables for pDPN- or PHN-Specific Medications and Expenditures

Variable	Marginal Effect (SE) <sup>a</sup>	z Score	P>z	95% Confidence Limits
<b>Medication Use Probability</b>				
Pregabalin	-0.050 (0.013)	-3.94	<.001	-0.075, -0.025
Opioid analgesics	-0.023 (0.023)	-1.02	.31	-0.068, 0.022
Nonopioid analgesics	-0.052 (0.021)	-2.49	.01	-0.092, -0.011
Anticonvulsants <sup>b</sup>	0.037 (0.017)	2.15	.03	0.003, 0.070
Antidepressants	-0.001 (0.018)	-0.07	.95	-0.036, 0.033
<b>pDPN- or PHN-related Expenditures, 2007 \$</b>				
Medication, \$	-63.40 (55.14)	-1.15	.25	-171.47, 44.66
Total, \$	-52.48 (63.25)	-0.83	.41	-176.45, 71.49

pDPN indicates painful diabetic peripheral neuropathy; PHN, postherpetic neuralgia.  
<sup>a</sup>Marginal effects are the adjusted annual effects for the 2006 follow-up year. Standard errors of the marginal effects were computed using the delta method.  
<sup>b</sup>Anticonvulsant use probability is exclusive of pregabalin use.

over year for PA plans. No other unadjusted differences in expenditures for pDPN- or PHN-related medications were statistically significant. Total pDPN- or PHN-related medication expenditures per member (including pregabalin) increased year over year in the non-PA plans by \$59 ( $P = .08$ ) and decreased in the PA plans by \$20 ( $P = .54$ ); however, the net unadjusted difference of \$79 less spent in PA plans was not statistically significant ( $P = .09$ ). The marginal effect resulting from multivariable modeling (Table 6) for pDPN- or PHN-related medication costs year over year showed no difference between cohorts (\$63 lower expenditures for PA plans,  $P = .25$ ).

The mean unadjusted pDPN- or PHN-specific total health-care expenditures increased by \$45 ( $P = .37$ ) per member during the postindex follow-up period compared with calendar year 2005 for non-PA plans and decreased by \$11 ( $P = .79$ ) for PA plans; however, the net lower cost difference for PA plans of \$56 per patient ( $P = .40$ ) was not statistically significant (Table 5). The marginal effect resulting from multivariable analysis (Table 6) showed that, controlling for baseline patient characteristics, there were no differences between cohorts for pDPN- or PHN-specific total health-care expenditures (\$52 lower pDPN- or PHN-specific total expenditures for PA plans,  $P = .41$ ).

## DISCUSSION

This study compared 2 cohorts of commercially insured patients diagnosed with PHN or having neuropathic pain associated with DPN, and whose health insurance benefits differed in their use restrictions for pregabalin: one cohort's plans required PA for pregabalin, while the other cohort's

plans did not. The 2 cohorts differed at baseline in terms of age, geographic region, and insurance coverage but may also have differed in unobserved characteristics. With health plans commonly reevaluating their provision of services annually, numerous changes affecting healthcare coverage may have gone unobserved over the study period, which included the inception of Medicare Part D in 2006. To minimize contemporaneous effects of the Medicare change, this study included only patients in commercial health plans who were not receiving Medicare benefits. As in a prior study<sup>24</sup> of PA for pregabalin among Medicaid patients, we used a difference-in-differences design for adjusting baseline differences between the PA and non-PA plans to allow for the comparison of relative year-over-year differences, while isolating the effects of the PA policy.<sup>42,43</sup> However, we acknowledge that the difference-in-differences approach can account only for observed changes that were parallel across plans.

As hypothesized, PA was effective in decreasing the relative use of pregabalin in PA plans (adjusted 5.0–percentage point lower probability of opioid use during the postindex follow-up period for PA plans,  $P < .001$ ) and was effective in limiting pregabalin use among patients with pDPN or PHN. There also was a statistically significant increase of 3.7 percentage points in the probability of patients in PA plans using other anticonvulsants during the postindex follow-up period compared with patients in non-PA plans and a decrease of 5.2 percentage points in the use of nonopioid analgesics. However, no significant differences were found in the use of opioids or pDPN- or PHN-related antidepressants in unadjusted descriptive data or in models controlling for the potential confounding effects of age, sex, geographic region, health plan type, other chronic pain conditions, and comorbidities. Therefore,

these latter results do not support the hypothesis that health plans with pregabalin PAs are associated with higher utilization of other pDPN or PHN pharmacologic treatments. Although utilization of anticonvulsants other than pregabalin was higher in PA plans, utilization of other pDPN or PHN pain management therapies was lower (nonopioid analgesics) or not significantly different (opioids and antidepressants). These results differ from prior study<sup>24</sup> findings among Medicaid patients in which there was significantly higher utilization of opioids and other pDPN- or PHN-related medications in Medicaid states requiring PA for pregabalin. Any number of unobserved factors may account for the difference such as variations in health plan policies, pDPN or PHN treatment reimbursement supported by commercial health plans versus Medicaid, and unobserved patient population factors, including health services availability and patient awareness of treatment options. These factors remain to be investigated.

Despite lower pregabalin utilization and lower nonopioid analgesic utilization in PA plans, there were no statistically significant differences in pDPN- or PHN-related total medication costs, pDPN or PHN total costs, or all-cause costs between PA and non-PA plans year over year in the descriptive statistics or the regression models. Again, this result differs from a prior study<sup>24</sup> of PA for pregabalin among Medicaid patients in which the unadjusted descriptive statistics and the regression model showed a marginal effect for the PA restriction associated with significantly higher pDPN or PHN medication costs and total costs incurred in PA plans. The results in the present study do not support the hypothesis that pregabalin PA policies in restricted plans are associated with higher overall and disease-related healthcare service utilization and expenditures, but they provide evidence that the effect on medical and pharmacy expenditures may provide no net cost savings.

Other studies<sup>12-15,46</sup> of PA effects have shown positive correlations with medication expenditure reductions. No cost reductions were found herein for pDPN or PHN resulting from the institution of PA policies for pregabalin in commercial health plans or Medicaid plans. To aid other investigators in further research, we have estimated that, given the marginal effect (SE) for pDPN- or PHN-specific total costs ( $-\$52.48$  [ $\$63.25$ ]) given in Table 6, a sample size of 38,809 would be required to yield a power of 80% (alternatively, a sample of 20,210 would yield a power of 80% for analysis of pDPN- or PHN-specific medication costs given the marginal effect [SE] of  $-\$63.40$  [ $\$55.14$ ]). To assist managed care decision makers in the selection of cost-reduction strategies, further investigation is needed to determine under what circumstances PA is effective in reducing disease-related expenditures.

## Limitations

This study is limited by the fact that only 12 health plans were included; nonetheless, the plans were grouped into those with versus without a PA policy, so associations between PA policies and drug utilization could be compared across plans. In the absence of randomization, it is impossible to establish the causal effect of PA on the pDPN or PHN treatment practices observed in this study. Observed differences in utilization patterns across plans stratified by PA status may reflect other elements of the insurance benefit design or patient characteristics rather than whether the plan had a PA policy in place for pregabalin; however, the difference-in-differences approach reduces this bias. Claims analyses are limited in their ability to account for all possible differences in patients and providers residing in different geographic regions. In addition, misclassification error is possible when relying on diagnosis coding from administrative claims data, for which the extent of undercoding or overcoding for DPN and PHN is unknown. This analysis focused on pregabalin use for pDPN and PHN, and the results should not be interpreted outside of these indications. With no specific diagnosis code for pDPN or PHN, this study relied on pharmaceutical claims for pain treatment after DPN or PHN diagnosis for identifying patients with painful manifestations of their condition. In the absence of diagnosis coding on pharmacy claims, it was assumed that the drugs shown to be used for treating pDPN or PHN (Table 1) were actually used as such. Health plan restrictions (PA, step therapy, tier differences, etc) for pDPN- or PHN-related medications other than pregabalin were not incorporated in the analysis. The administrative costs of the PA programs, which may vary across plans, were not considered in this analysis.

## CONCLUSIONS

This study explored the effect of PA policies for pregabalin in pDPNs and PHNs on healthcare utilization and expenditures in commercial health plans, comparing plans with versus without PA policies. The plans with PA policies restricting pregabalin access had a significantly lower proportion of patients with any pregabalin use compared with the plans without PA policies. Through the use of a difference-in-differences modeling approach with calculation of marginal effects, the restriction was shown to be associated with increased probability of other anticonvulsant use, decreased use of nonopioid analgesics, and no statistically significant differences in the use of opioids, antidepressants, or other drugs used to treat pDPN or PHN. The differences in medication utilization did not have a statistically significant effect on disease-related medication expenditures, disease-related total expenditures,



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or all-cause expenditures. Although the PA policy accomplished the objective of controlling access to pregabalin, the overall effect was a shift in the use of medications for treating pDPN or PHN, with no net cost savings.

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