Impact of a Novel Cost-Saving Pharmacy Program on Pregabalin Use and Health Care Costs

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ABSTRACT

BACKGROUND: Pharmacy cost-saving programs often aim to reduce costs for members and payers by encouraging use of lower-tier or generic medications and lower-cost sales channels. In 2010, a national U.S. health plan began a novel pharmacy program directed at reducing pharmacy expenditures for targeted medications, including pregabalin. The program provided multiple options to avoid higher cost sharing: use mail order pharmacy or switch to a lower-cost alternative medication via mail order or retail. Members who did not choose any option eventually paid the full retail cost of pregabalin.

OBJECTIVE: To evaluate the impact of the pharmacy program on pregabalin and alternative medication use, health care costs, and health care utilization.

METHODS: This retrospective analysis of claims data included adult commercial health plan members with a retail claim for pregabalin in the first 13 months of the pharmacy program (identification [ID] period: February 1, 2010–February 28, 2011). Members whose benefit plan included the pharmacy program were assigned to the program cohort; all others were assigned to the nonprogram cohort. The program cohort index date was the first retail pregabalin claim during the ID period and after the program start; the nonprogram cohort index date was the first retail pregabalin claim during the ID period. All members were continuously enrolled for 12 months pre- and post-index and had at least 1 inpatient claim or ≥ 2 ambulatory visit claims for a pregabalin-indicated condition.

Cohorts were propensity score matched (PSM) 1:1 with logistic regression on demographic and pre-index characteristics, including mail order and pregabalin use, comorbidity, health care costs, and health care utilization. Pregabalin, gabapentin and other alternative medication use, health care costs, and health care utilization were measured. The program cohort was also divided into 2 groups: members who changed to gabapentin post-index and those who did not.

A difference-in-differences (DiD) analysis was used to compare the between-cohort change in pregabalin and alternative medication use patterns, health care costs, and health care resource utilization from pre- to post-index. The within-cohort change from pre- to post-index was analyzed by McNemar's test (categorical variables) or paired t-test (continuous variables). The Rao-Scott chi-square test (categorical) and general estimating equations (continuous) were used to analyze between-cohort differences at each time point. Differences in program member characteristics of those who changed versus those who did not change to gabapentin post-index were assessed by traditional chi-square test (categorical) or two-sample t-test (continuous variables).

RESULTS: A total of 1,218 members in each cohort were PSM. Mean age was 51 years, 76.7% were women, and the most common pregabalin-indicated condition was fibromyalgia (77.6%). After the program start, the mean number of pregabalin claims from mail order and retail combined

decreased in the program cohort from 4.7 pre-index to 3.8 post-index, and increased in the nonprogram cohort from 4.7 pre-index to 6.2 post-index (DiD, $P < 0.001$). Pregabalin mail order use increased from 3.1% to 48.1% of program members versus 2.8% to 9.4% of nonprogram members (DiD, $P < 0.001$). Program members were also more likely to change to the anti-convulsant gabapentin post-index than were nonprogram members (31.0% vs. 15.9%, $P < 0.001$). Mean total health care costs were similar between cohorts, and the pre- to post-index change did not differ between cohorts (DiD, $P = 0.474$). However, mean total pharmacy costs rose from pre-index to post-index by \$820 and \$790 in the program and nonprogram cohorts, respectively (both $P < 0.001$); the increase was similar between cohorts (DiD, $P = 0.888$). Program members who changed to gabapentin had a higher mean comorbidity score ($P = 0.001$) and greater post-index use of opioids, alternative medications, and health care resources ($P < 0.050$) than program members who did not change to gabapentin.

CONCLUSIONS: The pharmacy program increased mail order use of pregabalin but reduced pregabalin claims from any venue. Program members were more likely to change to gabapentin than were nonprogram members, and those who changed had higher comorbidity, use of alternative medication, and health care resources. Despite increased mail order use for pregabalin and greater change to gabapentin by program members, the pharmacy program was not cost saving with respect to mean pharmacy or total health care costs.

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What is already known about this subject

- Recent pharmacy programs aimed at controlling rising expenditures have focused on reducing copayments through formulary tier changes.
- Most programs have used a single intervention and have focused primarily on medications for cardiac and diabetic care for which a generic alternative is available.
- These programs have been widely studied and, while many have been effective in improving medication adherence, they have been largely cost neutral.

What this study adds

- This study evaluated the impact of a novel pharmacy program that provides members with multiple options to avoid higher cost sharing of targeted medications: use mail order pharmacy or switch to a lower-cost alternative medication via mail order or retail.

What this study adds (continued)

- Members who changed from pregabalin to gabapentin had a higher disease burden, use of alternative medications, and health care utilization.
- Despite a shift in pregabalin use from retail to mail order and greater use of gabapentin by program members, pharmacy costs increased after the program start. Total health care spending did not change.

With rising prescription drug spending,¹ pharmacy benefit managers and health plans have developed strategies to reduce or offset expenditures. Most cost-containment programs include interventions such as switching from retail to mail order pharmacy,^{2,3} prior authorization,⁴ step therapy,⁵ or formulary tier modifications.⁶⁻⁸ These programs are intended to reduce pharmacy costs for both members and payers by encouraging the use of lower-tier or generic medications and lower-cost sales channels. However, pharmacy cost savings typically are not evaluated in the context of overall health care spending.

Pharmacy programs that contain a cost-sharing component have been the most widely evaluated.⁹ While health plan savings in pharmacy costs have been realized when patient cost sharing increased,¹⁰ total health plan spending either did not decrease or it increased.¹¹⁻¹⁴

More recently, pharmacy programs that provide financial incentives, rather than penalties, to patients have been introduced. The goal of incentive programs is to increase medication adherence by providing lower patient cost-sharing options, and consequently, improving health outcomes with the expectation of lower overall spending.¹⁵

Although reducing or eliminating prescription copayments has been associated with improved medication adherence for covered drugs, these programs have been largely cost neutral to the health plan.¹⁶⁻¹⁹ Most studies of mandatory or incentivized pharmacy programs have focused on commonly used medications for diabetes and cardiac care for which a generic medication is also available. There is scarce information for other conditions, including those for which a generic medication is not available.

Chronic pain conditions and disorders, such as painful diabetic peripheral neuropathy (DPN), postherpetic neuralgia (PHN), and fibromyalgia, share common pharmacologic treatments that include opioids, antidepressants, and anticonvulsants.^{20,21} Lyrica, or branded pregabalin,²² is an anticonvulsant approved in the United States for neuropathic pain associated with DPN, PHN and spinal cord injury, fibromyalgia, and adjunctive therapy for adult partial onset seizures. However, some health plans have restricted access to pregabalin via prior

authorization^{23,24} and step therapy.²⁵ Although restricted access decreased use of pregabalin and increased use of some alternative medications, there was no impact on disease-specific^{23,24} or all-cause costs.²⁵ Programs that offer patients multiple options to avoid higher cost sharing, including branded pregabalin, have not been investigated.

In 2010, a national health plan began a novel cost-saving pharmacy program targeting selected tier 3 medications, including pregabalin,²² which was the focus of this study. Health plan members who fill medications targeted by the pharmacy program at retail pharmacies are provided two “grace fills,” after which they may change to mail order delivery of the targeted medication (including pregabalin) or change to a less costly alternative (generic or brand) medication via mail order or retail. Members who do not elect one of these options pay the full cost of the targeted medications charged by the retail pharmacy. Members are notified of these options at the point of sale and by letter and/or phone call after the first and second grace fills.

We hypothesized that the pharmacy program would encourage members to change from retail pharmacies to mail order for their pregabalin fills or change to alternative lower-cost medications such as gabapentin (either through mail order or retail venues). Our objective was to examine changes in pregabalin and alternative medication use patterns after the pharmacy program began and how these changes translated into total health care and pharmacy costs. Specifically, we used a large administrative claims database to examine the impact of this novel pharmacy benefit program on pregabalin and alternative medication use patterns, health care costs, and health care resource utilization.

Methods

Study Design and Data Source

This retrospective study used claims data from the Optum Research Database (ORD). ORD contains medical and pharmacy claims and enrollment information from a large U.S. health plan with national coverage. Patient- and provider-reported outcomes are not available in ORD. Medical claims data include *International Classification of Disease, Ninth Revision, Clinical Modification* (ICD-9-CM) diagnosis codes, site of service codes, and health plan- and patient-paid amounts from providers and facilities. Pharmacy claims encompass National Drug Code numbers for filled prescriptions, days supply, quantity of drug supplied, drug strength, and health plan- and patient-paid amounts. All study data were accessed using techniques compliant with the Health Insurance Portability and Accountability Act; therefore, a separate institutional review board approval was not sought.

Study Population and Cohort Assignment

The sample included commercial health plan members who were ≥19 years in 2010 and had at least 1 retail pharmacy

claim for pregabalin during the identification (ID) period (February 1, 2010–February 28, 2011). Benefit information was used to identify members in the pharmacy program, including the program start date for each member (the pharmacy program was implemented over several months so not all members were targeted at the same time). Members with a retail pregabalin claim during the ID period and after the pharmacy program start date were considered the “program” cohort; the date of the first retail pregabalin claim after the program start date was the index date. Members were subject to the program design immediately upon program start date; the program did not include a washout period.

Members whose benefit plan did not include the pharmacy program were assigned to the nonprogram cohort; their index date was the first retail pregabalin claim during the ID period. Members in both cohorts were continuously enrolled in the health plan for 12 months pre-index and 12 months post-index and had at least 1 inpatient claim or ≥ 2 ambulatory visit claims with an ICD-9-CM diagnosis code for DPN, fibromyalgia, PHN, or partial onset seizure (Appendix A, available in online article) during the pre-index period. Cost-saving options (mail order, alternative medication, or both) were available to members of both study cohorts before and after the implementation of the program.

Members whose pharmacy program status changed post-index or whose estimated average dose of pregabalin was >600 milligrams per day (the maximum approved dose for pregabalin²²) at any time were excluded. As an exploratory analysis, 2 subgroups within the program cohort were defined: members who changed from pregabalin to gabapentin during the post-index period, and members who did not. Inclusion in the change group required at least 1 claim for gabapentin post-index. Prior gabapentin use was not a study exclusion. Although specific alternative medications were not prescribed by the program, gabapentin was selected for this comparison because of its similar mechanism of action, generic (low cost) availability, and common use in step-therapy programs.

Study Measures

Member Characteristics. Member age, sex, and U.S. Census region of enrollment were determined on the index date. Pre-index clinical characteristics included pregabalin-indicated conditions (described above), Charlson Comorbidity Index score,²⁶ and the presence/absence of comorbid conditions,²⁷ defined as at least 1 claim for the condition at any site of service (Appendix A).

Outcomes. The primary outcomes were the pre- to post-index change between the program and nonprogram cohorts in pregabalin use patterns, alternative pain medication use, all-cause health care costs, and all-cause health care resource utilization. Pregabalin use patterns were assessed by the count of pregabalin claims and were further categorized by venue (retail

or mail order, as identified on the pharmacy claim) and the proportion of members using mail order for pregabalin fills. Use of alternative medications was defined by at least 1 claim for drug classes that may be prescribed for pain conditions: gabapentin, opioids (short- and long-acting), serotonin and norepinephrine reuptake inhibitors (SNRIs), selective serotonin reuptake inhibitors (SSRIs), and tricyclic antidepressants (TCAs; Appendix B, available in online article). Members with a gabapentin claim post-index were assumed to have changed from pregabalin to gabapentin because combination use of both drugs would not be expected. Thus, the focus of gabapentin use was on the post-index period because pregabalin use was not required for study inclusion during the pre-index period.

Costs, both medical and pharmacy, were computed as the combined health plan- and member-paid amounts and categorized as medical (sum of ambulatory, emergency room [ER], and inpatient costs), pharmacy, and total costs (medical plus pharmacy). All costs were inflation-adjusted to 2012 dollars.²⁸ All-cause use was calculated using medical claims data and categorized as ambulatory visits (physician office and outpatient facility), ER visits, and inpatient admissions.

We also defined post-index discontinuation of pregabalin as the first gap in pregabalin days supply >90 days computed from each prescription claim date and the number of days supply on the claim. A 30-day gap was a secondary discontinuation measure. The proportion of members filling a prescription for any medication by mail order in the pre-index and post-index periods was also assessed. As an exploratory analysis, we also examined the pre- and post-index characteristics of program members who changed from pregabalin to gabapentin in the post-index period.

Propensity Score Matching

Members in the nonprogram cohort were propensity score matched (PSM) 1:1 to program cohort members.²⁹ Independent variables considered for inclusion in the propensity score were characteristics where the between-cohort *P* value was ≤ 0.250 in pre-PSM comparisons or likely to have meaningful impact on primary outcome variables. The final logistic regression controlled for age (categorical), gender, U.S. Census region, pre-index Charlson Comorbidity Index score (categorical), binary indicators of pre-index fibromyalgia and DPN (the prevalent pregabalin-indicated conditions), count of pre-index pregabalin pharmacy claims (categorical), a binary indicator of pre-index mail order pregabalin use, proportion of total pre-index pharmacy claims obtained via mail order (categorical), a binary indicator of pre-index inpatient hospitalization, pre-index all-cause medical costs, and pre-index all-cause pharmacy costs (Appendix C, available in online article). The PSM was performed using nearest neighbor matching with the greedy algorithm³⁰ and required matching within 0.2 of the standard deviation of the logit of the propensity score.^{31,32}

FIGURE 1 Sample Selection

^aPregabalin-indicated conditions: diabetic peripheral neuropathy, fibromyalgia, postherpetic neuralgia, or partial onset seizure.
ID=identification.

Statistical Analysis

Between-cohort unmatched comparisons were assessed with traditional chi-square tests for categorical variables and two-sample t-tests using Satterthwaite adjustment for unequal variances where appropriate for continuous variables.³³ Between-cohort matched comparisons were assessed by the Rao-Scott chi-square test³⁴ for categorical variables and general estimating equations for continuous variables (independent working correlation structure, normal distribution, log link).

Within-cohort between time period comparisons (pre-index vs. post-index) were assessed using McNemar's test³³ for categorical variables and paired t-tests for continuous variables.

Within the program cohort, differences between members who changed to gabapentin and those who did not were com-

puted by traditional chi-square test for categorical variables and two-sample t-test for continuous variables.

The primary outcomes measures (pregabalin and alternative medication use, health care costs, and health care utilization) were analyzed using a difference-in-differences (DiD) approach³⁵ to compare the between-cohort change from pre-index to post-index. The DiD analyses adjusted for period (pre-index vs. post-index), cohort (program vs. nonprogram), and period by cohort interaction, and used robust errors to account for the correlation between multiple records per subject. The *P* value of interest in these analyses corresponds to the period by cohort interaction. A gamma distribution was used for cost measures, a negative binomial distribution was used for count

TABLE 1 Propensity Score Matched Pre-index Demographic and Clinical Characteristics by Study Cohort

Characteristic ^a	Pharmacy Program (n = 1,218)		Nonpharmacy Program (n = 1,218)		P Value ^b
Age, years, mean (SD)	50.6	(10.6)	51.3	(11.4)	0.080
Age groups, years, n (%)					0.823
18-29	55	(4.5)	45	(3.7)	
30-39	126	(10.3)	129	(10.6)	
40-49	334	(27.4)	324	(26.6)	
50-59	457	(37.5)	471	(38.7)	
≥60	246	(20.2)	249	(20.4)	
Female, n (%)	929	(76.3)	940	(77.2)	0.598
U.S. Census region, n (%)					0.847
Northeast	61	(5.0)	67	(5.5)	
Midwest	337	(27.7)	328	(26.9)	
South	639	(52.5)	632	(51.9)	
West	181	(14.9)	191	(15.7)	
Pregabalin-indicated condition, n (%)^c					
Diabetic peripheral neuropathy	203	(16.7)	211	(17.3)	0.666
Fibromyalgia	944	(77.5)	946	(77.7)	0.922
Postherpetic neuralgia	27	(2.2)	33	(2.7)	0.431
Partial onset seizure	96	(7.9)	81	(6.7)	0.252
Fibromyalgia, no diabetic peripheral neuropathy	920	(75.5)	920	(75.5)	1.000
Diabetic peripheral neuropathy, no fibromyalgia	168	(13.8)	175	(14.4)	0.682
Fibromyalgia and diabetic peripheral neuropathy	48	(3.9)	47	(3.9)	0.918
Charlson Comorbidity Index score categories, mean (SD)	1.04	(1.46)	1.08	(1.54)	0.454
Charlson Comorbidity Index score categories, n (%)					0.611
0	572	(47.0)	550	(45.2)	
1	349	(28.7)	365	(30.0)	
2	148	(12.2)	162	(13.3)	
3	73	(6.0)	61	(5.0)	
≥4	76	(6.2)	80	(6.6)	
Comorbid condition, n (%)^d					
Restless leg syndrome	38	(3.1)	39	(3.2)	0.907
Sleep disorders	334	(27.4)	344	(28.2)	0.650
Osteoarthritis/rheumatoid arthritis	482	(39.6)	507	(41.6)	0.290
Neck and back pain (includes low back pain)	838	(68.8)	865	(71.0)	0.235

^aAge as of year of index date. All other characteristics determined in the 365-day period prior to index date.^bRao-Scott chi-square test for categorical variables; general estimating equations for continuous variables.^cRequired ≥2 nondiagnostic outpatient claims or at least 1 inpatient claim for indicated condition.^dRequired at least 1 claim at any site of service for indicated condition.

SD=standard deviation.

variables (including pregabalin use), and a logistic distribution was used for binary measures. A log link was used for all measures. Independent working correlation structures were used in all generalized estimating equation models.

Results

Member Sample and Pre-index Characteristics

There were 4,528 members (1,218 program and 3,310 nonprogram members) who met the inclusion criteria (Figure 1). After PSM, all 1,218 program members were retained and matched 1:1 with nonprogram members. The PSM resulted in well-

matched cohorts (Table 1 and Appendix C). Among matched members, mean age was 51 years, and 76.7% were women (data not shown). The mean Charlson Comorbidity Index score was 1.06, and nearly half of members had a score of 0 (data not shown). The most common pregabalin-indicated condition was fibromyalgia, with similar proportions of members in the program (77.5%) and nonprogram cohorts (77.7%).

Pregabalin Use Patterns

Table 2 shows pregabalin and alternative medication use patterns before (pre-index) and after (post-index) program

TABLE 2 Pattern of Pregabalin and Other Medication Use in the Pre- and Post-index Period by Study Cohort

Medication	Pharmacy Program			Nonpharmacy Program			P Value (Program vs. Nonprogram)		
	Pre-index (n = 1,218)	Post-index (n = 1,218)	P Value ^a	Pre-index (n = 1,218)	Post-index (n = 1,218)	P Value ^a	Pre-index ^b	Post-index ^b	DiD ^c
Pregabalin									
Total (mail order + retail)									
n (%)	818 (67.2)	1,218 (100.0)		831 (68.2)	1,218 (100.0)		0.519	—	
Number of claims, all members	4.66 (4.56)	3.80 (2.64)		4.68 (4.58)	6.16 (4.36)		0.912	<0.001	
Retail ^d									
n (%)	813 (66.7)	1,218 (100.0)		822 (67.5)	1,218 (100.0)				
Number of claims, all members	4.60 (4.56)	2.46 (2.05)		4.61 (4.60)	5.96 (4.38)		0.931	<0.001	<0.001
Mail order ^e									
n (%)	38 (3.1)	586 (48.1)	<0.001	34 (2.8)	114 (9.4)	<0.001	0.586	<0.001	<0.001
Number of claims, all members	0.06 (0.39)	1.34 (1.67)		0.07 (0.46)	0.20 (0.73)		0.792	<0.001	<0.001
All medications, proportion of fills that are mail order (includes pregabalin)	0.04 (0.12)	0.10 (0.16)	<0.001	0.04 (0.12)	0.05 (0.13)	<0.001	0.469	<0.001	
Alternative medication									
Gabapentin									
n (%)	257 (21.1)	378 (31.0)		203 (16.7)	194 (15.9)		0.005	<0.001	<0.001
Days to gabapentin change post-index	—	114.3 (95.8)	—	—	136.7 (112.0)	—	—	0.018	
Any short-acting opioid use (at least 1 claim), n (%)	686 (56.3)	668 (54.8)	0.299	669 (54.9)	667 (54.8)	0.914	0.486	0.968	0.528
Any long-acting opioid use (at least 1 claim), n (%)	263 (21.6)	269 (22.1)	0.607	245 (20.1)	274 (22.5)	0.015	0.367	0.803	0.162
Any TCA use (at least 1 claim), n (%)	184 (15.1)	167 (13.7)	0.178	197 (16.2)	177 (14.5)	0.109	0.472	0.563	0.909
Any SSRI use (at least 1 claim), n (%)	367 (30.1)	336 (27.6)	0.020	365 (30.0)	374 (30.7)	0.467	0.931	0.090	0.026
Any SNRI use (at least 1 claim), n (%)	457 (37.5)	445 (36.5)	0.418	417 (34.2)	427 (35.1)	0.500	0.088	0.442	0.295

Note: All values in this table given as mean (SD) unless otherwise indicated.

^aMcNemar's test for categorical variables; paired t-test for continuous variables.

^bRao-Scott chi-square test for categorical variables; general estimating equations for continuous variables.

^cP value corresponds to the period × cohort interaction.

^dMean supply of pregabalin per retail claim was 30.0 days (pre-index) and 29.3 days (post-index) for the pharmacy program and 30.8 days (pre-index) and 30.3 days (post-index) for the nonpharmacy program.

^eMean supply of pregabalin per mail order claims was 76.3 days (pre-index) and 84.5 days (post-index) for the pharmacy program and 83.5 days (pre-index) and 86.2 days (post-index) for the nonpharmacy program.

SD = standard deviation; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.

implementation among program and nonprogram members. Before the program start, both cohorts were equally likely to have pre-index pregabalin claims from any (retail or mail order) venue (67.2% program vs. 68.2% nonprogram). The mean number of pregabalin claims was similar between the program and nonprogram cohort (4.66 vs. 4.68, $P=0.912$), and 99% of pregabalin claims in both cohorts were filled at retail pharmacies (4.60 vs. 4.61, $P=0.931$). The proportion of all medication fills from mail order was also similar between cohorts.

After program implementation, the mean number of claims for pregabalin from any venue decreased in the program cohort (pre-index 4.66, post-index 3.80) and increased in the nonprogram cohort (pre-index 4.68; post-index 6.16). The DiD analysis for the between-cohort change was significant ($P<0.001$). At the retail level, the mean number of pregabalin claims decreased in the program cohort from 4.60 to 2.46 and increased in the nonprogram cohort from 4.61 to 5.96 (DiD

analysis, $P<0.001$). Only 30.4% of program cohort members had retail pharmacy claims for pregabalin after the 2 grace fills provided under the program compared with 66.8% of the nonprogram cohort ($P<0.001$; data not shown). Program members were also more likely to discontinue pregabalin (from any venue) than were nonprogram members: 64% of program members versus 52% of nonprogram members discontinued based on a 90-day supply gap threshold and 84% versus 74% using a 30-day supply gap ($P<0.001$; data not shown).

The proportion of program members using mail-order pharmacy for pregabalin rose from 3.1% pre-index to 48.1% post-index compared with an increase from 2.8% to 9.4% among nonprogram members (DiD analysis, $P<0.001$). The mean number of mail order pregabalin claims also increased in both cohorts, but the rise was more pronounced among program (0.06 to 1.34) than nonprogram members (0.07 to 0.20) and the between-cohort change was significant (DiD analysis, $P<0.001$).

TABLE 3 All-Cause Health Care Costs and All-Cause Health Care Utilization in the Pre- and Post-index Period by Study Cohort

	Pharmacy Program			Nonpharmacy Program			P Value (Program vs. Nonprogram)		
	Pre-index (n = 1,218)	Post-index (n = 1,218)	P Value ^a	Pre-index (n = 1,218)	Post-index (n = 1,218)	P Value ^a	Pre-index ^b	Post-index ^b	DiD ^c
All-cause health care costs (\$)^d									
Total	28,895 (46,255)	27,663 (49,662)	0.403	29,448 (44,853)	29,612 (51,773)	0.901	0.762	0.333	0.474
Medical	21,861 (43,177)	19,810 (47,598)	0.163	22,384 (43,388)	21,758 (49,656)	0.629	0.762	0.311	0.449
Pharmacy	7,033 (8,760)	7,853 (9,268)	<0.001	7,064 (8,034)	7,854 (8,594)	<0.001	0.929	0.998	0.888
All-cause health care utilizations									
At least 1 office visit, n (%)	1,217 (99.9)	1,215 (99.8)	0.317	1,218 (100.0)	1,214 (99.7)	0.125 ^e	1.00 ^e	0.706	^f
At least 1 outpatient visit, n (%)	988 (81.1)	973 (79.9)	0.378	1,020 (83.7)	987 (81.0)	0.039	0.087	0.480	0.392
At least 1 ER visit, n (%)	594 (48.8)	558 (45.8)	0.090	638 (52.4)	565 (46.4)	<0.001	0.077	0.775	0.212
At least 1 inpatient stay, n (%)	270 (22.2)	211 (17.3)	<0.001	279 (22.9)	288 (23.7)	0.610	0.643	<0.001	0.004
Number of all-cause health care utilizations									
Office visits	24.12 (17.56)	23.46 (17.64)	0.115	26.71 (20.30)	24.43 (19.74)	<0.001	<0.001	0.193	0.015
Outpatient visits	8.81 (11.88)	8.58 (12.42)	0.453	9.24 (12.17)	9.05 (12.70)	0.572	0.378	0.350	0.913
ER visits	2.39 (6.00)	2.19 (6.07)	0.242	2.50 (6.23)	2.08 (5.48)	0.009	0.643	0.635	0.319
Inpatient stays	0.36 (0.85)	0.29 (0.89)	0.025	0.40 (1.35)	0.37 (0.97)	0.267	0.280	0.046	0.402

Note: All values in this table given as mean (SD) unless otherwise indicated.

^aMcNemar's test for categorical variables; paired t-test for continuous variables.

^bRao-Scott chi-square test for categorical variables; general estimating equations for continuous variables.

^cP value corresponds to the period × cohort interaction.

^dInflation-adjusted to 2012 dollars.

^eExact binomial test.

^fDifference-in-differences P value could not be calculated using logistic regression for this variable because at least 1 cell had a value of 100.0%.

ER = emergency room; SD = standard deviation.

Alternative Medication Use Patterns

After the program start, program members were more likely to change from pregabalin to gabapentin than were nonprogram members (31.0% vs. 15.9%, $P < 0.001$) and make the change to gabapentin more quickly than nonprogram members (114.3 days vs. 136.7 days, $P = 0.018$). Table 2 shows that the use of long-acting opioids, short-acting opioids, SNRIs, and TCAs did not change significantly between cohorts (DiD analysis: $P \geq 0.162$). SSRI use declined modestly in the program cohort and increased slightly in the nonprogram cohort (DiD analysis: $P = 0.026$).

Health Care Costs and Utilization

All-cause total medical and pharmacy costs were similar for both cohorts in both the pre-index and post-index periods (Table 3). The pre-index to post-index change in both medical costs (DiD analysis: $P = 0.449$) and total costs (DiD analysis: $P = 0.474$) between cohorts was not significant. Although mean pharmacy costs rose significantly from pre-index to post-index by \$820 and \$790 in the program and nonprogram cohorts ($P < 0.001$), respectively, the increase in pharmacy costs was similar between cohorts (DiD analysis: $P = 0.888$).

Pre-index resource utilization was similar between cohorts for both the proportion of members using each service category and the mean count of encounters, with the exception of the mean count of pre-index office visits, which was higher in the nonprogram cohort. The pre- to post-index change in the proportion of members using inpatient services was significant (DiD analysis: $P = 0.004$) as a result of a post-index decline in the likelihood of inpatient service use among program members and a slight increase among nonprogram members with inpatient service use. The pre-index to post-index change in the count of resource utilizations was significant only for office visits (DiD analysis: $P = 0.015$) as a result of a larger post-index decline among nonprogram members compared with program members.

Characteristics of Program Members Who Changed to Gabapentin

Among both cohorts, 378 program members and 194 nonprogram members had evidence of changing from pregabalin to gabapentin after the pharmacy program began. The characteristics of pharmacy program members who changed to gabapentin versus those who did not change to gabapentin are shown in Table 4.

TABLE 4 Characteristics of Pharmacy Program Members Who Changed Versus Members Who Did Not Change from Pregabalin to Gabapentin in the Post-index Period

	Pharmacy Program: Pre-index Characteristics			Pharmacy Program: Post-index Characteristics		
	Change to Gabapentin		P Value ^a	Change to Gabapentin		P Value ^a
	Yes (n = 378)	No (n = 840)		Yes (n = 378)	No (n = 840)	
Age, years	51.7 (10.7)	50.1 (10.5)	0.015			
Female, n (%)	279 (73.8)	650 (77.4)	0.175			
Charlson Comorbidity Index score	1.25 (1.60)	0.94 (1.38)	0.001			
Pregabalin-indicated condition, ^b n (%)						
Diabetic peripheral neuropathy	87 (23.0)	116 (13.8)	<0.001			
Fibromyalgia	280 (74.1)	664 (79.1)	0.054			
Postherpetic neuralgia	5 (1.3)	22 (2.6)	0.155			
Partial onset seizure	17 (4.5)	79 (9.4)	0.003			
Any opioid use (at least 1 claim, short- or long-acting), n (%)	241 (63.8)	497 (59.2)	0.129	240 (63.5)	481 (57.3)	0.041
Any TCA use (at least 1 claim), n (%)	59 (15.6)	125 (14.9)	0.743	65 (17.2)	102 (12.1)	0.018
Any SSRI use (at least 1 claim), n (%)	127 (33.6)	240 (28.6)	0.077	120 (31.8)	216 (25.7)	0.029
Any SNRI use (at least 1 claim), n (%)	136 (36.0)	321 (38.2)	0.456	133 (35.2)	312 (37.1)	0.512
All-cause health care costs (\$)						
Total	33,328 (59,948)	26,900 (42,789)	0.038	32,241 (59,951)	25,603 (44,145)	0.054
Medical	25,871 (49,694)	20,057 (39,800)	0.046	23,975 (58,180)	17,936 (41,880)	0.070
Pharmacy	7,458 (11,084)	6,842 (7,482)	0.326	8,266 (10,654)	7,667 (8,573)	0.336
All-cause health care utilizations						
At least 1 office visit, n (%)	377 (99.7)	840 (100.0)	0.136	377 (99.7)	838 (99.8)	0.931
At least 1 outpatient visit, n (%)	308 (81.5)	680 (81.0)	0.827	317 (83.9)	656 (78.1)	0.020
At least 1 ER visit, n (%)	195 (51.6)	399 (47.5)	0.187	193 (51.1)	365 (43.5)	0.014
At least 1 inpatient stay, n (%)	98 (25.9)	172 (20.5)	0.034	87 (23.0)	124 (14.8)	<0.001
Number of all-cause health care utilizations						
Office visits	25.48 (17.91)	23.51 (17.38)	0.069	25.84 (19.75)	22.39 (16.50)	0.003
Outpatient visits	10.42 (15.13)	8.08 (10.01)	0.006	10.59 (15.25)	7.68 (10.80)	<0.001
ER visits	2.86 (6.77)	2.17 (5.62)	0.085	2.27 (6.32)	2.16 (5.96)	0.775
Inpatient stays	0.41 (0.84)	0.33 (0.86)	0.160	0.37 (0.82)	0.26 (0.92)	0.054

Note: All values in this table given as mean (SD) unless otherwise indicated.

^aTraditional chi-square test for categorical variables; two-sample t-test for continuous variables with Satterthwaite adjustment for unequal variances where appropriate.

^bRequired ≥ 2 nondiagnostic outpatient claims or at least 1 inpatient claim for indicated condition.

ER=emergency room; SD=standard deviation; SNRI=serotonin and norepinephrine reuptake inhibitor; SSRI=selective serotonin reuptake inhibitor; TCA=tricyclic antidepressant.

Pharmacy program members who changed to gabapentin were more likely to have a pre-index diagnosis of DPN and less likely to have a pre-index diagnosis of partial onset seizure than were program members who did not change ($P \leq 0.003$). Members who changed also had higher mean pre-index Charlson Comorbidity Index scores (1.25 vs. 0.94; $P = 0.001$) and greater pre-index total health care costs (\$33,328 vs. \$26,900; $P = 0.038$). After the pharmacy program began, program members who changed to gabapentin were more likely to use short- or long-acting opioids ($P = 0.041$), TCAs ($P = 0.018$), and SSRIs ($P = 0.029$) than were program members who did not change. The likelihood of outpatient, ER, and inpatient resource utilization and the mean count of office and outpatient visits were also higher among pharmacy program members who changed to gabapentin ($P \leq 0.020$).

Discussion

This study evaluated the impact of a novel pharmacy program that provided members using retail pregabalin with multiple options to avoid higher cost sharing after pharmacy benefit change. The results show the program's impact on pregabalin and alternative medication use.

Prior to the pharmacy program implementation, pregabalin use from any venue was similar among program and nonprogram members. However, after the pharmacy program began, mail order pregabalin use increased to a much greater extent among program members than nonprogram members.

While retail pregabalin use declined in the program cohort, nonprogram members increased their pregabalin use from retail venues. The pharmacy program also affected alternative medication use; twice as many program members changed to gabapentin compared with nonprogram members.

Despite members' behavior changes that should have contributed to reduced costs for those in the pharmacy program, pharmacy costs actually increased to a similar extent among program and nonprogram members, while total health care costs did not change significantly.

Our results are consistent with prior studies that have shown a largely neutral total cost impact when patient cost sharing increased or decreased.¹¹⁻¹⁹ Although mean pregabalin use declined in the pharmacy program cohort as a result of a higher proportion of pharmacy program members changing to gabapentin, this change did not translate to lower mean total health care costs.

These findings mirror the results of a multiemployer study in North Carolina that found reduced use of inpatient services (but higher medication adherence) after instituting a reduced-cost pharmacy program for medications commonly used in chronic conditions; yet the insurer's \$5.7 million decline in nondrug spending was not fully offset by the \$6.4 million increase in drug spending.¹⁸

Studies of single employer plans that provided lower member cost-sharing programs via reduced copayments have also been cost neutral for total spending,¹⁵⁻¹⁷ with the exception of a plan that coupled reduced cost sharing with disease management among diabetic patients and demonstrated a positive return on investment.³⁶

Program members were more likely to discontinue pregabalin and change to gabapentin, which is consistent with previous studies of higher cost-sharing pharmacy programs.^{10,37} When the pharmacy program cohort was stratified by members who changed to gabapentin versus those who did not, we found that members who changed had higher comorbidity scores; were more likely to use opioids, TCAs, or SSRIs; were higher health care users; and had higher costs. Further study is warranted to understand the circumstances that cause the higher-using/sicker members in the program to change from pregabalin to gabapentin.

Ultimately, changes in pharmacy benefit design must be judged in the context of both clinical and economic outcomes. More than 90% of the members in this study had a condition for which patient-reported outcomes, such as pain severity, should be a consideration for clinical management of the condition. These measures and the patient and physician rationale for switching to alternative medication use should be included in future studies to provide a more comprehensive assessment of the impact of pharmacy program changes that provide cost savings to members for alternative medication use.

Limitations

The ability of claims data to accurately capture an individual's medical and pharmacy history can be limited. Health care services that occurred before or after the study were not evaluated. We tracked utilization and costs for 12 months; cost sav-

ings may be realized with longer examination periods if the 12-month post-index period were extended well beyond the 60- to 90-day post-implementation window when most members were expected to select a cost-saving option.

This program was available only to commercially insured plans. The results may not be generalizable to public plans such as Medicare or Medicaid.

Additionally, benefit packages are often customized to specific employer groups. Our study used a general benefit package identifier to determine pharmacy program eligibility. Some employer groups could have had customized agreements that were not captured in the available data, resulting in incorrect attribution to a study cohort. We expect this miscapture to happen infrequently and to be equally applicable to the miscapture of members in either of the study cohorts; it would therefore not be expected to bias the outcomes. Additional unobservable differences between the study cohorts may have influenced the findings that could not be included in this analysis.

Finally, this was an independent analysis of a pharmacy program implemented by a large health plan. The study investigators had no role in the design or execution of the pharmacy program. The metrics by which the relative success or failure of the pharmacy program were judged were not available to the investigators of this study.

Conclusions

A novel pharmacy cost-saving program affected use of pregabalin but did not change overall health care costs. As the literature suggests, this program was effective in increasing use of mail order pregabalin and use of gabapentin as an alternative medication. Members who changed from pregabalin to gabapentin were sicker and higher health care users. While the overall objective of the pharmacy program was to reduce costs by changing member use of retail pregabalin to less expensive options, no cost savings were observed in the first year after the pharmacy program was implemented.

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DISCLOSURES

This study was sponsored by Pfizer. The results of this study were presented in part as posters at AMCP Nexus 2014, October 7-10, Boston, MA. Odell, Cappelleri, and Sadosky are employees of Pfizer. Martin, Bancroft, and Halpern are employees of Optum and were paid consultants to Pfizer in connection with developing this manuscript. None of the authors were affiliated with the design, implementation, or operations of the pharmacy program evaluated in this study.

Concept and design were performed by Odell, Halpern, and Martin, with assistance from the other authors. Data were analyzed by Bancroft. All authors interpreted the data. Martin wrote the manuscript with assistance from the other authors. All authors participated in manuscript review and revisions.

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APPENDIX A ICD-9-CM Diagnostic Codes for Identification of Pregabalin-Indicated Conditions and Other Comorbid Conditions

Pregabalin-Indicated Conditions	ICD-9-CM Code
Diabetic peripheral neuropathy	250.6x or 357.2
Fibromyalgia	729.1
Postherpetic neuralgia	053.1x
Partial onset seizure	345.4x, 345.5x, 345.7x or 780.39
Other Comorbid Conditions	
Restless leg syndrome	333.94
Sleep disorders	780.5x, 347.x, 307.4x, V69.4
Arthritis (includes rheumatoid arthritis and other arthropathies)	710.xx, 711.xx, 712.xx, 713.xx, 714.xx (except 714.3), 715.xx, 717.xx, 718.xx
Neck and back pain	720.xx, 721.xx (except 721.1 and 721.91), 722.xx (except 722.0, 722.2, and 722.7x), 723.x (except 723.4), 724.xx (except 724.3 and 724.4), 737.1x, 737.2x, 737.30 (excludes 737.0x and 737.31+), 738.4, 739.0, 739.1, 739.2, 739.3, 739.4, 756.xx, 805.4, 805.6, 805.8, 846.x, 847.x

ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification.

APPENDIX B Alternative Pain Medication Drug Classes and Drugs

Drug Class	Included Drugs
Short-acting opioids	butorphanol, codeine, dihydrocodeine, hydrocodone, levorphanol, levomethadyl, meperidine, pentazocine, propoxyphene
Long-acting opioids	buprenorphine, methadone
Short- and long-acting opioids	fentanyl, hydromorphone, morphine, oxycodone, oxymorphone, tramadol, tapentadol
Selective serotonin reuptake inhibitors	citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine
Serotonin and norepinephrine reuptake inhibitors	desvenlafaxine, duloxetine, milnacipran, venlafaxine
Tricyclic antidepressants and related compounds	amitriptyline, amitriptyline/chlordiazepoxide, amitriptyline/perphenazine, amoxapine, clomipramine, desipramine, doxepin, imipramine, imipramine pamoate, maprotiline, nortriptyline, protriptyline, trimipramine

APPENDIX C Propensity Score Matching Variables Before and After Matching by Cohort

	Pre-Propensity Score Matching					Post-Propensity Score Matching				
	Pharmacy Program (N = 1,218)		Nonprogram (N=3,310)		Program versus Non- program P Value ^a	Pharmacy Program (N = 1,218)		Nonprogram (N = 1,218)		Program versus Non- program P Value ^b
	n	%	n	%		n	%	n	%	
Age group, years					<0.001					0.823
18-29	55	4.52	121	3.66		55	4.52	45	3.69	
30-39	126	10.34	408	12.33		126	10.34	129	10.59	
40-49	334	27.42	815	24.62		334	27.42	324	26.60	
50-59	457	37.52	1,075	32.48		457	37.52	471	38.67	
60+	246	20.20	891	26.92		246	20.20	249	20.44	
Gender					0.619					0.598
Female	929	76.27	2,501	75.56		929	76.27	940	77.18	
Male	289	23.73	809	24.44		289	23.73	278	22.82	
U.S. Census region					<0.001					0.847
Northeast	61	5.01	285	8.61		61	5.01	67	5.50	
Midwest	337	27.67	682	20.60		337	27.67	328	26.93	
South	639	52.46	1,838	55.53		639	52.46	632	51.89	
West	181	14.86	505	15.26		181	14.86	191	15.68	
Pre-index Charlson Comorbidity Index score					0.041					0.611
0	572	46.96	1,500	45.32		572	46.96	550	45.16	
1	349	28.65	864	26.10		349	28.65	365	29.97	
2	148	12.15	443	13.38		148	12.15	162	13.30	
3	73	5.99	224	6.77		73	5.99	61	5.01	
≥4	76	6.24	279	8.43		76	6.24	80	6.57	
Pre-index pregabalin-indicated condition^b										
Diabetic peripheral neuropathy	203	16.67	639	19.31	0.043	203	16.67	211	17.32	0.666
Fibromyalgia	944	77.50	2,458	74.26	0.025	944	77.50	946	77.67	0.922
Count of pre-index pregabalin claims					<0.001					
0	400	32.84	1,355	40.94		400	32.84	387	31.77	0.821
1-5	323	26.52	900	27.19		323	26.52	330	27.09	
≥6	495	40.64	1,055	31.87		495	40.64	501	41.13	
Any pre-index mail order pregabalin use (at least 1 claim)	38	3.12	191	5.77	<0.001	38	3.12	34	2.79	0.586
Proportion of total pre-index medication fills that are mail order					<0.001					0.598
No pre-index medication fills or no pre-index mail order medication fills	988	81.12	2,532	76.50		988	81.12	1,008	82.76	
0.000-0.125 ^c	88	7.22	239	7.22		88	7.22	84	6.90	
0.126-0.333 ^c	78	6.40	242	7.31		78	6.40	75	6.16	
≥0.334 ^c	64	5.25	297	8.97		64	5.25	51	4.19	
At least 1 inpatient hospitalization	270	22.17	883	26.68	0.002	270	22.17	279	22.91	0.643
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Pre-index medical costs (\$)	21,861	43,177	22,047	43,446	0.898	21,861	43,177	22,384	43,388	0.762
Pre-index pharmacy costs (\$)	7,033	8,760	6,676	8,139	0.215	7,033	8,760	7,064	8,034	0.929

^aTraditional chi-square tests for categorical variables; two-sample t-tests using appropriate degrees of freedom for continuous variables.

^bRao-Scott chi-square test for categorical variables; general estimating equations for continuous variables; z-tests using robust standard errors for continuous variables.

^cCategories contain roughly 33% of positive proportions.

SD = standard deviation.